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Review

The increasing challenge of genetic counseling for cystic fibrosis

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ABSTRACT

Genetic counseling for cystic fibrosis (CF) is challenged by intricate molecular mechanisms, complex phenotypes, and psychosocial needs. *CFTR* variant interpretation has become critical; this manuscript examines variant nomenclature and classes, as well as opportunities and challenges posed by genetic technologies and genotype-directed therapies. With post-graduate training in medical genetics and counseling, genetic counselors educate patients and families, facilitate testing and interpretation, and help integrate genetic information into diagnosis and treatment. They support families, ranging from carrier couples or new parents, to children understanding their disease, to adults with CF contemplating reproduction. The changing face of CF increasingly highlights the critical importance of genetic information to patients and their families. Genetic counselors are uniquely poised to translate this information in diagnostics and personalized care. Genetic counselors straddle molecular and clinical realms, helping patients adapt, plan, and gain access to appropriate therapies.

Contents

Abbreviations: ART, Assisted reproductive technology; CBAVD, Congenital bilateral absence of the vas deferens; cDNA, Complementary DNA; CF, Cystic fibrosis; CFF, Cystic Fibrosis Foundation; CFSPID, Cystic fibrosis screen positive, inconclusive diagnosis; *CFTR*, Cystic fibrosis transmembrane conductance regulator gene; CFTR, Cystic fibrosis transmembrane conductance regulator protein; CFTR-RD, CFTR-related disorder; CRISPR, Clustered regularly interspaced short palindromic repeats; CRMS, CFTR-related metabolic syndrome; DNA, Deoxyribonucleic acid; FDA, United States Food and Drug Administration; HGVS, Human Genome Variation Society.; IRT, Immuno-reactive trypsinogen; IVF, in vitro fertilization; mRNA, Messenger RNA; NBS, Newborn screening; PAP, Pancreatitis associated protein; PGD/PIGD, Preimplantation genetic diagnosis; PPV, Positive predictive value; RNA, Ribonucleic acid; SCT, Sweat chloride test; US, United States.

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1. Introduction

Cystic fibrosis (CF) is an autosomal recessive condition caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Frequently used as a basic genetics teaching example, counseling for CF is complex despite apparent genetic simplicity. Varied penetrance of *CFTR* variants makes phenotypic prediction challenging, and emergence of therapies addressing the underlying genetic defect are changing the clinical landscape. There has also been a change in nomenclature: healthcare professionals are familiar with the term *mutation*, which is more accurately termed a *causative variant* (the terminology used in this manuscript). In addition, there has been a move from the legacy system of describing variants by their impact on the protein product to the Human Genome Variation Society (HGVS) system, in which a variant is described by its change to the genetic code. In this paper we refer to variants first by HGVS name (also known as cDNA name) with legacy name in brackets, which is used thereafter. Terminology is reviewed in Table 1.

Cystic fibrosis is a multifaceted condition with wide clinical variability, hundreds of causative *CFTR* variants, and genotype-based treatments. The variant c.350G>A [R117H] is relatively common and an example of a variant resulting in varied penetrance, ranging from no phenotypic impact to CFTR-related disorder (CFTR-RD) to CF. While R117H is an extreme example, varied clinical impact is a feature of all *CFTR* variants. Collaborative resources, including Clinical and Functional Translation of CFTR (CFTR2) and CFTR-France, have been developed to collect and share genotype and phenotype information among researchers, clinicians, and patients.

The role of the genetic counselor spans all ages of CF care from preconception or prenatal testing, to newborn screening (NBS), and to support with treatment and decision-making later in life. The genetic counselor requires a wide skillset to place complex genetic principles in both medical and psychosocial frameworks [1,2].

Expert genomic knowledge is critical to translate genetic test results to improved care. Genetic counselors are healthcare professionals with post-graduate training in medical genetics and counseling. They provide information and support needed to understand genetic results and familial implications, adjust to a diagnosis, and make decisions that are medically sound yet suited to the patient or family's goals [1,2].

In this review, we describe the issues around *CFTR* gene testing and classification and the impact of results at different ages, reflecting on distinct roles of the genetic counselor at these times.

2. *CFTR* testing and interpretation

Reflecting increased ability to interrogate and interpret DNA changes, the CF diagnostic algorithm now incorporates *CFTR* molecular testing [4]. Identification of two causative variants is diagnostic for CF, even in the absence of a diagnostic sweat chloride, though a sweat chloride test (SCT) is still necessary [4]. Multiple testing methodologies are widely available and are summarized in Table 2. Genetic counselors are well-poised to evaluate test utility, including considerations of patient ethnicity, clinical presentation, cost, insurance coverage, turnaround time, and intended use of results. Studies in other conditions have found that genetic counselor involvement in molecular test selection significantly reduces errors and cost [2,8].

A genetic counselor is valuable for interpreting and explaining results, both straightforward and complex. Complex examples include situations in which more than one (in carrier screening) or two (in diagnostic testing) variants are identified, assessment of an at-risk fetus, interpretation of variants affected by in *cis* changes (e.g. R117H and polyT), and scenarios in which disease liability of a variant is unknown or variable. Follow-up testing, evaluation, and counseling for the patient and family are often warranted. Case 1 (Table 3) illustrates the importance of incorporating genotype into diagnosis and treatment, even in atypical presentation.

Table 1
Terminology [3–7].

Term	Definition
Cystic fibrosis (CF)	• A CF diagnosis can be made in individuals who have at least one feature/finding from both categories below: • A: CLINICAL FEATURES B: LABORATORY FINDINGS • -Clinical symptoms consistent with CF -Sweat chloride ≥60 mmol/L • -A positive newborn screen −2 CF-causing variants in *trans* • -Family history of CF -Abnormal nasal potential difference
CFTR-related metabolic syndrome (CRMS)/ cystic fibrosis screen positive, inconclusive diagnosis (CFSPID)	CRMS (United States) and CFSPID (other countries) are terms applied to infants with a positive newborn screen for CF who do not have clinical features of CF. Individuals with CRMS/CFSPID must have a positive newborn screen and either: - a sweat chloride <30 mmol/L and 2 *CFTR* variants where at least 1 has unclear phenotypic consequences OR - an intermediate sweat chloride (30–59 mmol/L) and 1 or 0 CF-causing mutations
CFTR-related disorder	A monosystem clinical entity (e.g. CBAVD, pancreatitis, bronchiectasis) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF
CFTR variant	Differences from the accepted or reference DNA sequence of the *CFTR* gene; may or may not be harmful
CFTR mutation	In some instances, the term *mutation* has been used interchangeably with *variant* to describe any change from the reference DNA sequence. More correctly, *mutation* refers only to pathogenic sequence variations. Recently, *variant* has become the preferred term for all sequence variations with disease liability designated.
CF-causing variant/ causative variant	A variant expected to cause CF when present in *trans* with another CF-causing variant
Variant of varying clinical consequence (VCC)	A variant that may or may not result in CF when present in *trans* with a CF-causing variant
Non CF-causing variant	A variant not expected to result in CF when present in *trans* with a CF-causing variant. Most individuals with this type of variant combination will be healthy. A small number of individuals may develop mild symptoms or be diagnosed with a CFTR-related disorder, but symptoms are not expected to meet the definition of CF.
Variant of uncertain significance	At this time, it is uncertain whether the variant is disease-causing or not
Complex allele	A single *CFTR* gene containing more than one variant; Several well-known examples include: c.1727G > G and c.2002C > T [G576A and R668C], c.1521_1523delCTT and c.3080 T > C [F508del and I1027T], and c.220C > T and c.3808G > A [R74W and D1270N]
Cis configuration	The occurrence of more than one variant within the same *CFTR* gene, i.e. a complex allele with both variants inherited from one parent
Trans configuration	The occurrence of bi-allelic variants; a *CFTR* variant was inherited from each parent. CF occurs due to causative variants in *trans* configuration
Genetic counselor	A professional with post-graduate training in medical genetics and counseling to interpret genetic test results and provide personalized patient guidance and support
Genetic counseling	The process of helping people understand and adapt to genetic contributions to disease, including impacts on the individual and family

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Table 2
Types of *CFTR* genetic testing.

Type of CFTR genetic test	Capabilities and limitations	Most appropriate for
CFTR variant panel	Detects specific variants on the panel and no others, often the most common variants in the Caucasian population; Widely variable detection rate dependent on ethnic background and panel makeup	Routine carrier screening for those with no family history of CF; patients with a clear CF diagnosis who are Ashkenazi Jewish or European Caucasian; commonly used genetic testing in newborn screening algorithms
Traditional sequencing (i.e. Sanger sequencing)	Detects all sequence changes in exons and intron-exon junctions of *CFTR*; does not detect large deletions or duplications	Patients with a CF diagnosis who are not Ashkenazi Jewish or European Caucasian, or who have fewer than two mutations identified from panel testing; may be utilized as a carrier screen when one partner is affected or a known carrier especially in the setting of non-Caucasian ethnicity.
Deletion / duplication analysis	Detects large deletions and duplications involving all or part of exons in *CFTR*; does not detect sequence changes	Patients with a CF diagnosis who have had fewer than two CF-causing variants identified after *CFTR* sequencing
Next-generation sequencing	Detects sequence changes in exons and intron-exon junctions of *CFTR*; does not detect large deletions or duplications *without specific further analysis by laboratory* (some - but not all - labs offer this)	Patients with a CF diagnosis who are not Ashkenazi Jewish or European Caucasian, or who have fewer than two CF--causing variants identified from panel testing; may be utilized as a carrier screen when one partner is affected or a known carrier especially in the setting of non--Caucasian ethnicity; may be utilized in screening algorithms if a multi-step reveal of results is required
Targeted familial variant testing	Detects only one or two specific variants that have been previously identified in a family	Determines presence or absence of specific variant(s) in close relatives of a patient or carrier; useful for parent or sibling follow-up testing

3. Classifying *CFTR* variants

CFTR variants have been previously classified according to molecular impact. Class I variants result in no useful transcription of protein, including: variants resulting in a premature stop codon (nonsense variants, ending in X in legacy nomenclature); variants affecting canonical splice sites (+1 and −1 positions adjacent to exons); and variants leading to large deletions. Class II variants result in transcription of full-length but abnormal protein that is misfolded or incorrectly trafficked to the cell membrane. For class III variants, full-length protein is transcribed and correctly located but does not function. Class IV variants produce a protein that reaches the cell surface but has decreased chloride conductance. Class V variants produce a reduced quantity of functional CFTR protein, often due to mis-splicing, and Class VI variants produce a less stable CFTR molecule (Fig. 1). Recently, it has been suggested that Class I variants are divided into those with a premature stop codon, which may be amenable to read-through correction by small molecules, and those with no CFTR production (deletions or large duplications; suggested terms for this group are Class VII or Class Zero) which are likely not amenable to small molecule correction [9].

Patients and families are increasingly interested in their variant information and classification. Drug development has fostered a tendency to describe variants by their potential response to small molecule therapies. Class III variants are widely referred to as gating variants, which are expected to respond to a potentiator such as ivacaftor. Other classes have been grouped as either minimal function (class I-II) or residual function (class IV-VI) (Fig. 1) [10], although this oversimplifies a complex situation and varied response to new therapies has demonstrated that some variants may straddle a number of classes.

The challenge of characterizing numerous variants underscores the importance of understanding their molecular impact. Genetic counselors can advise families on functional classes and whether therapies are available.

Table 3
Cases.

Case 1. AF is a 13-year-old competitive dancer who was healthy until age 10, when she developed a chronic cough after viral illness. Standard asthma treatments failed and symptoms worsened. Allergy and immunology workups were negative. Over the next two years chest radiographs progressed from peri-hilar infiltrates to bronchiectasis, and she was referred to pulmonology. Testing revealed intermediate SCT at 37 mmol/L and two causative *CFTR* variants: c.3718-2477C > T [3849 + 10kbC > T] and c.1680-886A > G [1811 + 1634A > G]. In further evaluation she was pancreatic sufficient with one prior episode of pancreatitis, and respiratory cultures were positive for *Staphylococcus aureus*. Several CF-specific respiratory treatments were initiated with marked improvement in symptoms. She has recently started tezacaftor/ivacaftor combination therapy.	Case 2. TS is a 4-week-old male deemed a carrier of c.1521_1523delCTT [F508del] following positive NBS and subsequent normal SCT (<30 mmol/L). Parental carrier testing found that his mother is an F508del carrier. Family history was reviewed and was significant for a maternal uncle with recurrent pancreatitis. With knowledge of a familial *CFTR* variant and possibly related disease, this uncle underwent evaluation where SCT was 70 mmol/L and variant analysis identified F508del and R117H 7 T/9 T, establishing the diagnosis of CF. Insight was provided for another uncle with infertility. The same F508del and R117H 7 T/9 T genotype was confirmed, as well as CBAVD, with SCT of 29 mmol/L. In the absence of other symptoms, a CFTR-RD diagnosis was established. This genetic counseling case demonstrates variable expression of the genotype within the family and the medical utility of obtaining family history.

4. Diagnostic dilemmas

Diagnostic dilemmas are frustrating for patients and providers. While genetic testing has improved diagnostic ability, it requires that a) two *CFTR* variants are identified in *trans*, and b) both variants are known to cause CF. Over 2000 variants have been identified in *CFTR* (http://www.genet.sickkids.on.ca/cftr/), but only 336 have been rigorously studied and defined as CF-causing [5]. Interpretation of rare and variable consequence variants remains challenging. Genetic counselors work alongside providers to define diagnoses in uncertain situations and are trained to synthesize available information, provide educated interpretation of some variants with unknown liability, and provide insight for well-described variants with variable consequences (Case 2).

Intermediate SCT results (30–59 mmol/L), symptoms not unique to CF, or fewer than two CF-causing variants pose clinical challenges. Genetic counselors are adept in considering other etiologies if CF is not confirmed and symptoms overlap other conditions. The most commonly-discussed differential diagnoses are primary ciliary dyskinesia, non-CF bronchiectasis, pseudohypoaldosteronism, and Shwachman-Diamond syndrome. In the absence of an alternative diagnosis, individuals with unclear presentations are difficult to diagnose or dismiss from CF care. Uncertainty can have a significant psychological impact on a patient or family and genetic counselors can provide the necessary emotional support [18]. Furthermore, genetic counselors can contribute to ongoing care of individuals with unusual presentations of CF, CFTR-RD, or CRMS/CFSPID by regularly reviewing databases such as CFTR2 for new variant interpretations and clinical information.

5. Prenatal

American College of Obstetrics and Gynecology (ACOG) guidelines (2011) recommend that CF carrier screening be offered to all women who are pregnant or considering pregnancy [19]. A common variant

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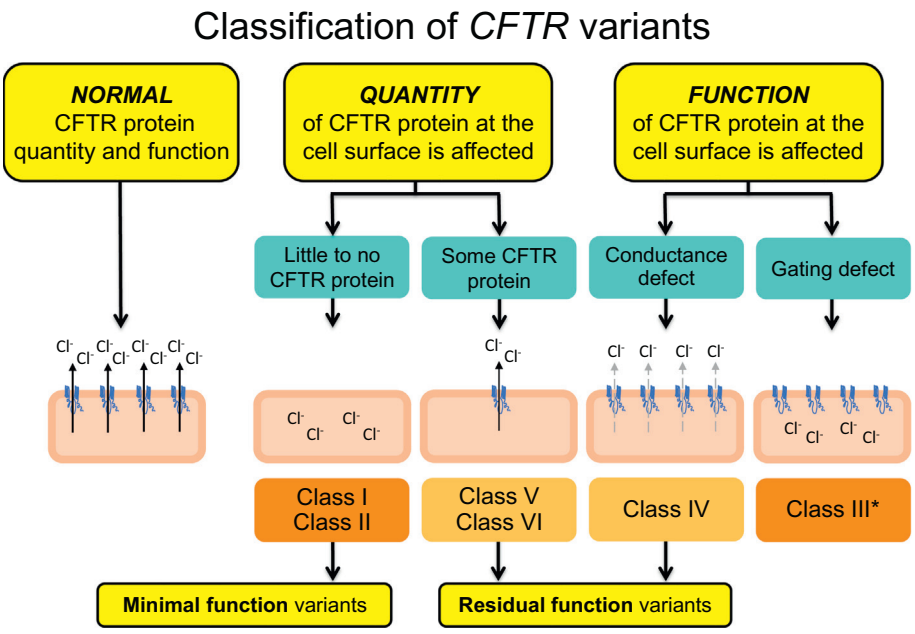

Fig. 1. The schematic represents the amount of CFTR protein in the cell membrane and the impact on function (illustrated by the movement of chloride ions (Cl-) out of the cell). Classification of CFTR mutations: minimal function (class I-II) and residual function (class IV-VI) [10–17]. *Class III mutations are known as gating variants because they may respond to a potentiator such as ivacaftor. Examples of variants for each class (HGVS name [legacy name]): Class I: c.1624G>T [G542X]; Class II: c.1521_1523delCTT [F508del]; Class III: c.1652G>A [G551D]; Class IV: c.350G>A [R117H]; Class V: c.3718-2477C>T [3849+10kbC>T]; Class VI: c.120del123 [252del123].

panel is recommended instead of *CFTR* sequencing, though actual practice varies. The concept of residual risk after carrier screening should be discussed, as many patients assume negative screening eliminates carrier risk. However, screening is not always accompanied by genetic counseling, particularly in the setting of negative results. Sensitivity for the common 23-variant panel in the US varies by ethnicity, ranging from ~49% in Asians to ~94% in Ashkenazi Jews [20]. Without appropriate counseling, it can be surprising and distressing if an affected child is born after negative carrier screening. Discrepancies may also exist between carrier screening panels and those used in NBS; some infants may be found by NBS to carry a variant not interrogated by parental screening.

A study of CF patients' attitudes toward carrier screening found that >80% supported preconception carrier screening [21]; still, the greatest uptake of carrier screening is among pregnant couples, often through their obstetrician. Approximately 69% of couples screened through population-based carrier screening in Australia were pregnant at the time of testing [21,22].

When a carrier is identified, partner testing options include a variant panel or *CFTR* sequencing. Counseling should include discussion of the benefits and limitations of each technology, as well as costs, turnaround time, and the possibility of identifying variants of uncertain significance, if reported by the laboratory. Testing both members of a couple concurrently with a panel provides results quickly; however some may seek additional testing if one partner has a positive finding. For example, the residual risk to be a carrier after a negative 23-variant panel is ~1 in 200 for a Caucasian, non-Jewish individual. If his/her partner is a carrier, the residual risk to have an affected child is 1 in 800. By contrast, negative sequencing reduces the same patient's carrier risk to ~1 in 2700, resulting in a reproductive risk of 1 in 10,800. While some providers offer high sensitivity variant panels or sequencing for partner testing, advanced testing may not be covered by insurance, and the possibility of discovering a variant of uncertain significance should be discussed, if applicable.

Carrier screening is available through numerous laboratories. Next generation sequencing (NGS) allows hundreds of genes to be sequenced simultaneously for carrier screening, often at the same out-of-pocket cost as *CFTR* panel testing alone. Known as *expanded carrier screening*, CF carrier screening in this context poses challenges. Typically, expanded carrier screening panels do not report variants of uncertain significance (only pathogenic or likely pathogenic variants) and still require a discussion of residual risk. Genetic counselors are tasked with explaining screening that may include hundreds of conditions, making it difficult to describe each in detail. As a result, patients are surprised to receive positive results when there is no family history of the condition or they did not have full knowledge of conditions tested [23].

Prenatal concern for CF may also arise due to hyperechoic bowel on prenatal ultrasound. Among many etiologies, fetal hyperechoic bowel can be caused by altered meconium consistency in the small intestine resulting from pancreatic enzyme secretion abnormalities. Hyperechoic bowel has been reported in 50–78% of fetuses with known CF, and the finding of hyperechoic bowel in a fetus without previously known CF risk is associated with a 0.8–13.3% chance for CF, depending on parental ethnicity and other factors [24]. Therefore, this finding should prompt discussion of CF and parental carrier screening if not already performed.

Most carrier couples have no family history of CF, no prior knowledge of the condition, and require substantial education. A study of prenatal genetic counselors' preparedness to discuss CF with carrier couples found "the majority of counselors would 'definitely' discuss physical health (94.2%), life expectancy (86.4%) and treatment burden (70.8%), while less than a quarter would 'definitely' discuss psychological and emotional health (22.7%) or social functioning and personal goal fulfillment (24%)." Genetic counselors in prenatal settings often did not feel knowledgeable discussing newer CF treatments and expressed the need to refer to a CF specialist [25].

Preimplantation genetic diagnosis (PGD/PIGD) is an option for carrier couples; it involves embryo biopsy and genetic testing for known parental variants after embryos are achieved using in vitro fertilization. Prospective parents may choose embryo transfer of only those without the disease-causing genotype. European Society of Human Reproduction and Embryology (ESHRE) PGD consortium data show that CF accounts for ~10% of indications for monogenic disorders [26]. Genetic counselors and CF specialists are often asked in the preconception or prenatal timeframe to predict phenotype based on genotype. Registries and databases aid in this task, yet couples should be informed of the range of outcomes associated with any genotype [26]. Carrier couples

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may face difficult choices of whether to pursue PGD, or, in the event of current pregnancy, invasive prenatal diagnostic testing and possibly pregnancy termination. Appropriate counseling by a clinician with CF expertise may help avoid termination of pregnancy when a fetus has a non CF-causing variant or variant associated with mild disease. Some countries restrict which conditions or variants are acceptable for PGD; this option may not be available for some families carrying a variant of varying clinical consequence [27].

6. Newborn screening

Newborn screening for CF is a successful public health strategy for early recognition of affected infants, facilitating proactive treatment [28]. This strategy has been adopted by most countries in which the prevalence of CF is high. All programs utilize measurement of immuno-reactive trypsinogen (IRT) from a dried bloodspot sample collected in the first week of life, followed by a second tier of testing, which often includes molecular analysis for *CFTR* variants (Table 4) [29]. Inclusion of DNA testing improves specificity and timeliness, particularly when two variants are identified. DNA testing is generally performed on the initial sample with variant panels targeted at the population being screened. This streamlined protocol is especially beneficial in regions where geography or resources limit collection of a second dried bloodspot sample. Incorporation of DNA testing increases recognition of CF carriers, as these infants have higher IRT values [30]. In most programs, a normal SCT (<30 mmol/L) is used to report that CF is unlikely. In some programs, a repeat IRT measurement at day-of-life 10–21 is used to avoid the need for SCT if the result is normal.

Some programs have attempted to reduce carrier recognition and improve positive predictive value (PPV) using pancreatitis associated protein (PAP) and/or extended gene analysis through *CFTR* sequencing [31]. Extended gene analysis as a third-tier test significantly improves PPV but increases detection of variants of unknown significance. In these cases, SCT is important to evaluate physiological evidence of CF; however, if the result is normal or intermediate, uncertainty remains. Because variable penetrance of some *CFTR* variants is well-recognized, a portion of these well infants are at risk for CFTR-RD or CF later in life. Infants with an inconclusive diagnostic evaluation after positive NBS have been designated CFTR-related metabolic syndrome (CRMS) in the US and CF screen positive, inconclusive diagnosis (CFSPID) in other countries. It is important to appreciate that the risk for disease in these otherwise well infants is difficult to quantify.

Genetic counseling for families of an infant with CRMS/CFSPID should include: a) carrier status education; b) family planning discussion; c) documentation of family history; and d) ensuring extensive genotyping for diagnostic purposes, particularly in the case of an intermediate SCT (30–59 mmol/L). In certain situations, it is unclear if an infant is a carrier or has CRMS/CFSPID and parental testing is necessary to determine if an infant's variants are in *cis* or *trans*. In the situation of a screen-positive infant with a normal SCT (<30 mmol/L) and fewer than two CF-causing variants in *trans*, CF is unlikely [32]. Infants with an intermediate SCT result have higher risk of being reclassified as CF, but the majority remain well [33]. A study of infants with CFSPID from Canada and Italy demonstrated 11% reclassification to CF due to an increase in SCT to >60 mmol/L and/or change in variant classification on the CFTR2 website [4]. A California study of children with CRMS with (TG)13-5 T and a CF-causing variant found 38% reclassification to CF in the first 8 years of life based on SCT and clinical presentation [34].

An unknown percentage of infants with CRMS/CFSPID may be at risk for future CFTR-RD, which describes a single-organ condition that relates to CFTR dysfunction but does not meet CF diagnostic criteria [35]. This classification typically includes congenital bilateral absence of the vas deferens (CBAVD) in males, pancreatitis, or bronchiectasis. There is no doubt that infants with CRMS/CFSPID have an increased a priori risk of CFTR-RD, though risk is difficult to quantify.

When an infant with CRMS/CFSPID develops CF-related symptoms such as chronic cough, there is a tendency to diagnose initially with CFTR-RD, rather than CF [36]. While understandable, these children still have some risk to meet CF diagnostic criteria later in life. It is important that infants in this situation receive appropriate CF care and that families receive relevant information. Because phenotype, symptoms, or diagnoses may change years after initial counseling, written materials are helpful for parents [37].

Genetic counselors have a number of roles within NBS programs. For infants recognized as carriers (false positive NBS), a genetic counselor may be the only healthcare professional outside of primary care to address this result. The genetic counselor provides parents with information on CF carrier testing, risks for future pregnancies, and cascade screening for family members. Support and education by a genetic counselor reduce parental long-term stress [38]. It is also important to address ownership of genetic information and how and when families should relay genetic results to their child. There is limited research and no consensus guideline on disclosure of carrier status to children; one study of Fragile X carriers suggested that disclosure occur during teenage years [39]. While more research is needed, a genetic counselor is well-poised to work through the process with a family.

For infants diagnosed with CF after NBS, genetic counselor involvement may occur after parental adjustment. In other cases, the genetic counselor facilitates diagnostic understanding or delivers the diagnosis. If a genetic counselor is not involved upfront, a referral should be provided, as genetic counselors provide parents with support and important information about recurrence and familial risk. Some genetic counselors work closely with or within the CF team, which has advantages: staying connected to the ever-changing CF world and having in-depth knowledge of *CFTR* variants and therapies. In other services, the genetic counselor is separate from the CF team. This offers other advantages: the family may feel more comfortable discussing reproductive decisions with a professional independent of their CF team [38,39].

Table 4
Description of different models of CF newborn screening [30–32,35,38,40–49].

Model	Sensitivity	PPV	Pros	Cons
IRT/IRT	76%	5–16%	May be appropriate in countries with a low incidence of F508del	Low specificity (high false positive rates); Requires collection of second sample
IRT/PAP	80%	5–10%	Lowest detection of carriers; No second sample needed	Low specificity (high false positive rates)
IRT/PAP/DNA/Seq	95%	88%	Highest PPV and specificity; Low carrier detection; No second sample needed	More costly; Identifies variants of uncertain significance (increased CRMS/CFSPID)
IRT/DNA/IRT	97%	65%	Very high specificity	Requires second sample
IRT/IRT/DNA	96%	27%	High specificity	Requires second sample
IRT/DNA	95–98%	9%	Most commonly used protocol; Improves timeliness; No second sample needed	High carrier detection; Low specificity (high false positives); Results the highest number of referrals for sweat testing
IRT/DNA/Seq	92%	34%	High specificity; Improves detection in ethnically diverse populations; No second sample needed; Lowest number of referrals for sweat testing	Increases the detection of carriers and CRMS/CFSPID

Legend: IRT- Immuno-reactive trypsinogen; PAP- pancreatitis associated protein; DNA refers to a *CFTR* variant panel (variants tested differ among programs); Seq - *CFTR* gene sequencing, which can use Sanger or next-generation sequencing

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7. Pediatric

Genetic testing is a critical step in obtaining complete diagnostic information for an infant or child with CF, which guides treatment at increasingly earlier ages. Genetic counselors advise on test selection and explain inheritance and results to parents of a newly diagnosed child, and later to the child his- or herself.

Children with CF have varied genetic counseling needs in different developmental stages. The question, "Why do I have CF?" is an opportunity for age-appropriate explanations about genes and inheritance. Adolescents may be exposed to CF genetics through their studies in school and have corresponding questions. Anticipatory discussions of the child's preference for disclosure of diagnosis to classmates during school years may be warranted, as this topic can be sensitive and preferences differ. Teens with CF should have staged education on fertility, recurrence risk, assisted reproductive technologies (ART), and partner carrier testing, in addition to routine sexual health education. Studies indicate that parents and patients wish to have conversations about sexual and reproductive health with healthcare providers by age 14, which is often earlier than reported experiences [50,51]. It is important to consider preferences of parents and patients in relaying this information; incorporating genetic counseling early in this process provides a robust framework on which education from the CF team can be placed.

A CF diagnosis has implications for siblings and family planning. Genetic counseling at regular intervals allows for timely, accurate, supportive, and non-directive information on recurrence risk and reproductive options. Facilitation and affirmation of parental decision-making are vital in these situations.

United States Cystic Fibrosis Foundation (CFF) guidelines recommend that "families of infants diagnosed with CF should receive appropriate education at the first diagnostic visit, and genetic counseling should be provided [3]." A SCT should be performed on first-degree siblings and on half-siblings with CF symptoms [3,52]. Approaches to sibling testing vary; most clinicians recommend a SCT but some opt for familial variant testing instead or in addition [53]. In the event of a negative SCT, the sibling has a 2/3 (66%) chance of being a carrier. It is important to convey that SCT does not determine carrier status. Carrier testing in children is not supported by many professional organizations [54]. Still, many parents request sibling carrier testing and can be frustrated if refused, so careful counseling is required [55,56]. If carrier testing is performed, pre- and post-test genetic counseling is essential. When the proband's CF genotype is associated with variable SCT values <60 mmol/L (e.g. R117H), special consideration should be given to the diagnostic capabilities and limitations of both SCT and familial variant testing.

8. Adult

Although most CF patients are diagnosed as children, more than half of individuals living with CF are adults. Increasing life expectancy and better health allow many adults with CF to fully engage in careers, hobbies, family, and enjoy a high quality of life [57]. Educational and support needs throughout adulthood encompass sexual health and family planning, emotional and relational issues, and wellness strategies.

Education about reproductive options helps adults with CF achieve relational and family goals. Informed decision-making and exploring risks and benefits are central to the process of genetic counseling. Before conception planning, adults with CF should understand their physiologic ability to have children, risk for disease recurrence (50% if partner is a carrier; partner carrier testing should be offered), and review personal goals and health status. A partner's negative carrier screen significantly reduces risk of an affected child, and residual risk should be addressed. Burdens of treatment time and cost, reality of caring for self and child, and possible death of a parent before a child is grown may affect family planning. Decisions regarding whether and how to become parents are complex. Options include biological parenthood, ART with or without PGD, gamete donation or surrogacy, adoption, or the choice not to have children. Regardless of parenthood plans, adults should be informed and have discussions about sexual health in CF with a knowledgeable team member.

Over 95% of males with CF are infertile due to CBAVD; however, viable sperm can be retrieved from >90% of infertile men with CF for use in IVF [58]. Most females may achieve natural pregnancy, though thicker cervical mucosa or poor nutritional status can impair fertility. Genetic counselors are familiar with fertility processes and reproductive options and can guide the education and decision-making process, including necessary specialist referrals.

As more females with CF become pregnant, care teams should discuss pregnancy planning and safety in CF, addressing questions about effects on short- and long-term health. Factors to consider include: maternal lung function, nutritional and pancreatic sufficiency status, CF-related diabetes, maternal risks for increased exacerbation frequency and gestational hypertension, and fetal risk for preterm birth and low birth weight. Despite these risks, maternal outcomes for women with CF are generally good. No difference has been shown between 10-year survival rates for females with CF who carried a pregnancy and matched controls with CF who did not [59]. More recently, a small case-control study showed no effect of pregnancy on nutritional outcomes, changes in lung function, or exacerbation rates during a 4.5 year period [60].

Individuals diagnosed as adults (~4–5% of CF patients) are a unique cohort. Improved genetic testing, lower threshold of normal SCT values (<30 mmol/L), and recognition of a broader clinical spectrum allow ascertainment of older individuals with milder or later onset symptoms, often related to milder *CFTR* variants. Currently, those diagnosed in adulthood were typically born before CF NBS and may represent an age-advanced CRMS/CFSPID cohort that is well during childhood with later conversion. These individuals benefit from genetic counseling as well, addressing subjects classically discussed in a childhood diagnosis.

Mental health is now recognized as a critical issue in CF, with 2016 CFF guidelines recommending that all adolescents (12+) and adults with CF be screened for symptoms of depression and anxiety [61]. Genetic counselors have training in psychosocial assessment and counseling and can assist with annual screening and wellness needs.

9. CFTR therapies

The year 2012 marked a significant milestone in CF care, with approval in the US of a molecular therapy, ivacaftor, that corrects the defective CFTR protein bearing the variant c.1652G>A [G551D] [62], with approval in other countries soon after. Clinical trials of ivacaftor demonstrated immediate, significant, and sustained clinical benefit with increased FEV1, decreased sweat chloride, and decreased pulmonary exacerbation frequency [63–66]. While knowledge of an individual's genotype was previously helpful for diagnosis, prognosis, and research purposes, it became essential for ensuring optimal treatment. Additional compounds have received approval in some countries (lumacaftor-ivacaftor and tezacaftor-ivacaftor) and are available for patients with over 40 specific variants. Ongoing clinical trials are evaluating long-term effects of modulator treatments and efficacy for other genotypes, underscoring the importance of correct variant identification and interpretation in all patients. Research continues to develop compounds to treat a greater number of *CFTR* variants, although F508del remains the prime focus, as nearly 90% of people with CF have at least one copy of this variant.

A small percentage of individuals carry two variants that result in no CFTR protein production (nonsense, canonical splice, exon deletions, etc.). The early promise of read-through agents, such as ataluren, that prevent use of premature termination codons, has not been realized and the ataluren research program has not moved forward [67]. At present, there are no molecular therapies to address these variants and attention has moved to alternative strategies such as gene replacement

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or editing. One such strategy, the CRISPR/Cas9 system, has been explored for some *CFTR* variants [68]. This technique shows promise in the laboratory but has not yet progressed to clinical trials. Additional gene- or RNA-targeted therapies include antisense oligonucleotides, some of which are in early-stage clinical trials, and gene replacement therapy using liposomes, which has been investigated in large clinical trials with some minimal evidence of efficacy [69]. These approaches offer some promise to correct the underlying genetic defect in people with CF, but are not yet at a stage that impacts genetic counseling advice.

Genetic counselors can assist providers and patients in identifying personalized treatment options and research studies. In the US, the role of a CF genetic counselor may include identifying appropriate molecular treatment or clinical trials for an individual, explaining the molecular mechanism of treatments, or discussing potential effects of treatments upon fertility or pregnancy, though these duties vary among clinics. For example, genetic counselors in CF clinics or maternal-fetal medicine practice will highlight complications such as the reduced effectiveness of hormonal contraception with lumacaftor-ivacaftor, and potential teratogenic effects of other CF treatments. Coupled with expertise in family planning options, a genetic counselor can help balance modulator eligibility with personal needs and goals.

Counseling on life expectancy for those with CF now needs to take into account the emergence of new therapies. Genetic counseling in the prenatal setting for someone carrying a variant such as G551D with an approved and effective molecular therapy is different than for someone who carries a nonsense variant for which no treatment is available.

10. Professional issues

Genetic counselor involvement differs among CF centers, with some genetic counselors also working with patient registry data, study coordination, and group education. Genetic counselors have unique perspectives of viewing the patient, immediate, and extended family as a whole. Patient confidentiality is emphasized; yet in heritable diagnoses, patients should be provided with information about the mode of inheritance, associated risks, and appropriate screening and intervention options for family members [70]. Genetic counselors are skilled at assessing and discussing familial risk, ensuring the patient is equipped to share recommendations with relatives (e.g. through a family share letter).

CF centers that have a genetic counselor in clinic find it beneficial to the team and patients [71]. Others cite cost, logistics, and availability as barriers to incorporating a genetic counselor. Convenient and timely access to genetic counselors can be challenging, as a relative shortage of genetic counselors exists compared to clinical need. National genetic counselor organizations have ongoing efforts to examine workforce issues, particularly in direct patient care [72]. In the US, the genetic counselor workforce has grown 88–100% in the past 10 years, with continued projected growth of 72–100% in the next decade [6,73]. While this trend is encouraging, the current and projected increase in workforce may still not be enough to meet ideal clinical staffing needs. In the absence of an in-person genetic counselor, clinicians may consider a variety of other ways to deliver pertinent information. Telemedicine through hospital-based or contracted genetic counselors is becoming more widely available in some areas [40,41]. For example, telephone genetic counseling is offered by the California NBS program. Having this resource is better than none, but consumer-driven utilization of this service has been only 12% [28]. CF providers may also find it necessary to provide genetics education and basic counseling in CF clinic, including explanation of inheritance, the patient's genotype, and discussion of recurrence risk. In these situations especially, having patient materials to distribute may be helpful. Because genetics and genetic counseling can be quite complex, it is important that patients and families have an opportunity to engage with a genetic counselor, particularly one who specializes in CF.

Inconsistent billing and reimbursement for genetic counselor services is sometimes also an issue in some parts of the US and other countries. In the US, despite American Medical Association (AMA) approval of the billing code for "medical genetics and genetic counseling services," reimbursement varies with factors such as credentialing and state licensure [74]. Federal advocacy efforts aim to "improve access to quality genetic counseling and ensure the genetic counseling profession is a recognized and integral part of the healthcare system" [6]. It is hopeful that with improved reimbursement, CF patients and families will have increased genetic counselor access over time.

11. Conclusion

Genetic counselors understand the implications of genetic results and can translate these concepts to people with CF, their families, and care team. This spans from helping patients and families understand their diagnosis to processing complex decisions; genetic counselor support and expertise are needed throughout the increasing lifespan. Having dual psychosocial and medical roles, genetic counselors provide an important bridge between scientific advancement and real-world application to improve CF lives and care.

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